ISMP Adverse Drug Reactions

Patient with Terbinafine-Induced Subacute Cutaneous Lupus Erythematosus Followed by Thalidomide-Induced Orofacial Neuropathy

Beta Blocker Use, Hypertension, and the Risk of Psoriasis

Eczematous Reaction to Intravenous Immunoglobulin

Nicolau Syndrome After Intra-Articular Glucocorticoid Injection

Troponin Leak Associated with Drug-Induced Methemoglobinemia

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MEDWATCH program (800-FDA-1088). If you have reported an interesting, preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MEDWATCH program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

PATIENT WITH TERBINAFINE-INDUCED SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS FOLLOWED BY THALIDOMIDE-INDUCED OROFACIAL NEUROPATHY

A 40-year-old female was seen by a physician for itchy rash after 2 months of treatment with oral terbinafine (*Lamisil*) for onychomycosis. Her medication history revealed she had discontinued terbinafine approximately 2 months earlier, however her red, itchy rash persisted. Her symptoms included the rash that involved her back, arms, and chest and

recent hair loss. The patient had a longstanding history of Raynaud phenomenon and photosensitivity, but denied fevers, arthritis, muscle weakness, and oral ulcers.

Upon physical exam, the patient was found to have annular erythematous plaques with peripheral scale on her chest, upper back, and arms. Laboratory tests revealed an antinuclear antibody titer of 1:320 (normal range < 1:40), elevated anti-SSA antibodies, and immunoglobulin G β 2-glycoprotein. Results of

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her urinalysis, complete blood count, and comprehensive metabolic panel were within normal limits. A punch biopsy specimen of a lesion on her right arm showed vacuolar interface dermatitis, dermal mucin deposition, and predominantly lymphocytic infiltrate along neurovascular structures in the superficial and deep dermis. Based on the collective findings, the patient was diagnosed with subacute cutaneous lupus erythematosus (SCLE).

SCLE is recognized as a distinct subset of cutaneous lupus. More than 100 medications have been implicated in causing SCLE, with terbinafine being one of the most commonly reported agents. Cutaneous findings of drug-induced SCLE are indistinguishable from those of non-drug-related disease. In some cases of drug-induced SCLE, symptoms resolve with discontinuation of the offending agent. When the cutaneous eruption persists, as in this patient, treatment is necessary.

The patient was initiated on hydroxychloroquine 400 mg daily, thalidomide 100 mg daily, and aspirin 81 mg daily. Thalidomide is a treatment option for patients who are resistant to first-line agents or for acute treatment prior to the onset of action of antimalarials. After 13 doses of thalidomide, the patient complained of numbness of her lips, tongue, and face. Her symptoms began with a tingling sensation of her upper and lower lips and expanded to involve her perioral face and tip of her tongue. These areas eventually became numb; there were no motor deficits and no other areas involved. The patient reported that all symptoms resolved upon discontinuation of thalidomide. Ten days later, she resumed use of thalidomide; three days after a single dose, her symptoms recurred in the same pattern but with a more rapid onset. The patient's paresthesias cleared within 2 days of thalidomide withdrawal and her skin lesions were significantly improved. Thalidomide was permanently discontinued, and the patient was continued on hydroxychloroquine 400 mg daily. The patient has not reported numbness in the 10 weeks since her last thalidomide dose.

The authors point out that potential adverse effects of thalidomide include birth defects, peripheral neuropathy, sedation, rash, constipation, dizziness, and thromboembolic complications. However the peripheral neuropathy that occurs is usually characterized by paresthesias and sensory loss of the distal extremities. The proposed theories of why thalidomide causes neuropathy include thalidomide-related toxic distal axonopathy, antiangiogenesis, dysregulation of

neurotrophic activity, and genetic predispositions. The prevalence of thalidomide neuropathy can be as high as 56%. Thirty-six percent of thalidomide-induced neuropathy cases are related to the use of thalidomide for the treatment of lupus erythematosus, with over 50% of patients discontinuing thalidomide therapy completely. Patients are more likely to develop neuropathy within the first year of therapy. The most important risk for thalidomide-induced neuropathy is the dose; neuropathy was not seen with the use of a thalidomide dose of less than 25 mg daily.

In analyzing the patient case, the authors note that while the thalidomide was only used for a short time, the symptoms cleared upon thalidomide discontinuation and recurred upon reinitiation. Neurotoxicity of the distal extremities is a known side effect of thalidomide, but this case represents the presentation of a patient who experienced orofacial neurotoxicity. The authors warn that clinicians should be aware of this phenomenon and discontinue thalidomide if it is the suspected culprit.

Anyanwu CO, Stewart CL, Werth VP. Thalidomide-induced orofacial neuropathy. *J Clin Rheum.* 2014;20(7):300-400.

BETA BLOCKER USE, HYPERTENSION, AND THE RISK OF PSORIASIS

A group of researchers (Miyamoto et al) evaluated the risk of psoriasis in patients with hypertension and tried to correlate this to the specific antihypertensive medications they received. They performed a prospective cohort study utilizing the volunteers who participated in the Nurse's Health Study. The study cohort consisted of 77,728 women who provided biennially updated data on hypertension and antihypertensive medications. The Nurse's Health Study was established in 1976 when 121,701 married, female registered nurses aged 30 to 55 years who were residing in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical history and lifestyle risk factors. This database has been utilized for numerous prospective cohort studies to research a variety of conditions.

The study cohort revealed 843 incident cases of psoriasis. The researchers found an increased risk of psoriasis among young women with a history of hypertension for a duration of 6 years or more. Specifically, hypertensive women without medication use and with current medication use were more likely to develop psoriasis compared with normotensive women without medication use. Among the

individual antihypertensive drugs, only beta blockers were associated with an increased risk of psoriasis after regular use for 6 years or more. Other widely used antihypertensive drugs, including thiazide diuretics, calcium channel blockers, and ACE inhibitors, were not associated with risk of psoriasis in the current study. However, analyses according to duration of regular medication use suggested trends toward increasing risk of psoriasis with the use of these medications.

The authors point out that psoriasis is a disease characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes and is classified as a T_H1 disease. Hypertension is also characterized by increased oxidative stress and inflammation, and immune mechanisms are reported to be involved in the development of hypertension, with different helper T cells (ie, T_H1 and T_H2 lymphocytes and T-regulatory cells) participating as pro- and anti-inflammatory cells. Prior research has found that chronic inflammation is associated with an increased incidence of hypertension. Therefore, hypertension may be associated with psoriasis development because of the shared inflammatory pathways.

The authors conclude that their research provides evidence that a prior history of long-term hypertension of 6 years or more was associated with an increased risk of psoriasis. Among individual antihypertensive drugs, only beta blockers were associated with an increased risk of psoriasis after long-term regular use for 6 years or more. These findings provide novel insights into the association among hypertension, antihypertensive medications, and psoriasis. The authors warn that more work needs to be done to confirm their findings and to investigate the biological mechanisms that underlie this process.

Wu S, Han J, Li WQ, et al. Hypertension, antihypertensive medication use and the risk of psoriasis. *JAMA Dermatol.* 2014;150(9):957-963.

ECZEMATOUS REACTION TO INTRAVENOUS IMMUNOGLOBULIN

A male who was in his 70s presented with eczematous plaques on his face, trunk, and extremities, including erythema, fissures, and scales on his palms and soles. His medical history revealed peripheral neuropathy due to Waldenstrom macroglobulinemia. Several days prior to the onset of his skin lesions, he had been treated with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg/day for 2 days for control of his neuropathy. The patient did not have history

of prior IVIG treatment, atopic dermatitis, respiratory allergies, and/or asthma. The patient's additional medications at the time were aspirin, simvastatin, and tamsulosin. These medications had remained unchanged for the past 2 years.

A skin biopsy was performed on lesional skin and histologic analysis showed spongiosis and lymphocytic infiltrates. Intracellular deposits of C3 throughout the epidermis and granular depositions along the basement membrane were found, however IgG or IgA were not detected. No serum antibodies against desmoglein-1, desmoglein-3, desmocollin-1, or envoplakin were detected. Serum antinuclear antibody titers were also negative. The patient was initially treated with topical corticosteroids and skin emollients, however the skin lesions persisted. Because the lesions persisted, the patient's treatment was switched to oral methylprednisone (0.3 mg/kg/day). The patient responded to this therapy, and his skin lesions cleared within 2 weeks. Following tapering and without further treatment, no recurrence was observed during a follow-up period of 3 years. Further IVIG therapy has been withheld despite persisting neuropathy.

Based on clinical examination, direct and indirect immunofluorescence (IF) microscopy, histologic, and laboratory findings, the authors diagnosed the patient with an eczematous reaction due to IVIG treatment. This reaction is often pronounced on the palms and soles. Usually topical steroids are effective treatment, but occasionally oral steroids are needed. The pathogenesis of the eczematous reactions to IVIG is known. Possible theories such as serum complement consumption have been reported. The authors point out that their patient exhibited epidermal complement deposits, which could be an explanation for this reaction in their patient. Also IVIG can act in a manner analogous to a β -cell superantigen, meaning that β -cells are activated following IVIG therapy. The authors speculate that activated β -cells may produce the antibodies against epidermal antigens.

Miyamoto J, Bockle BC, Zillikens D, et al. Eczematous reaction to intravenous immunoglobulin: An alternative cause of eczema. *JAMA Dermatol.* 2014;150(10):1120-1122.

NICOLAU SYNDROME AFTER INTRA-ARTICULAR GLUCOCORTICOID INJECTION

An 11-year-old boy with juvenile idiopathic arthritis was scheduled to receive a corticosteroid injection of his left ankle. The patient had received the same injection on 3 prior occasions without incident. A needle was inserted into the left ankle, and

no synovial fluid or blood was aspirated. A combination of lidocaine and methylprednisolone was injected into the joint space. Immediately after injection, the patient began to complain of severe pain. His foot and his toes distal to the injection site began to blanch. His foot was warm and he had easily palpable dorsalis pedis and posterior tibial pulses. The patient was then given ibuprofen and was observed for an hour. At this time, the patient's pain had subsided and the color had returned to his foot, however his toes remained pale and cool.

Over the next 12 to 15 hours, the patient developed a purple netlike rash with a branch-like extension. His rash progressed up from his toes and up his foot to include a portion of the leg proximal to the injection site. An ultrasound of the lower extremities did not show any superficial or deep vein thrombosis. Laboratory tests revealed a normal complete blood count, fibrinogen, coagulation profile, and only a mild elevation of the d-dimer. His serum creatinine kinase and myoglobin were unremarkable.

Therapy was initiated to restore perfusion to the affected limb. A combination of systemic and local vasodilators were utilized, including oral nifedipine, topical nitroglycerine, and warming of the extremity. The patient was subsequently anticoagulated with a heparin infusion and transitioned to a twice daily regimen of subcutaneous enoxaparin. Pentoxifylline, which is theorized to decrease blood viscosity, was administered to enhance peripheral perfusion and as an adjunct to vasodilator therapy. The patient was then discharged from the children's hospital to receive daily hyperbaric oxygen therapy at a local burn center.

After 10 days of treatment, the color in the proximal ankle had improved; however, the patient's toes remained purple and the patient maintained good motor controls of his toes. The patient had gradual improvement in his condition. Six months after the start of the reaction, the patient underwent debridement and skin grafting. The final result was the removal of the distal toe to the interphalangeal joint with an absent toenail.

The authors point out that the condition that the patient suffered from is known by multiple names, including livedoid dermatitis, embolia cutis medicamentosa, or Nicolau syndrome. The condition is an exceedingly rare complication of intra-articular or intramuscular injection of crystalloid suspensions. The condition is characterized by immediate pain at the injection site followed by pallor and eventual

development of a violet skin rash that can progress to soft tissue necrosis or rhabdomyolysis. This reaction has been documented with a variety of medications including nonsteroidal anti-inflammatory drugs, antibiotics, glucocorticoids, local anesthetics, and vitamins. Pediatric cases of Nicolau syndrome are very rare; in the literature, the reported cases have only been associated with an intramuscular injection. The possible mechanisms for this condition have been suggested as (a) localized sympathetic reactive vasospasm following intraarticular or perivascular injection, (b) arterial embolism of the crystalloid suspension, and (c) microvascular thrombosis.

The authors warn that because there is no standardized treatment for Nicolau syndrome, prevention is the best measure to avoid soft tissue necrosis. It is important that injection is performed in the least vascular area possible and that aspiration be performed before crystalloid injection into muscle or joint.

McKinney C, Sharma N, Jerath RS. Livedoid dermatitis (Nicolau syndrome) following intra-articular glucocorticoid injection. *J Clin Rheum.* 2014;20(6):339-340.

TROPONIN LEAK ASSOCIATED WITH DRUG-INDUCED METHEMOGLOBINEMIA

A 59-year-old Caucasian female presented to the emergency department (ED) with a chief complaint of abdominal pain for 36 hours. Her medical history was positive for chronic cystitis for several years, hypertension, hyperlipidemia, bipolar disorder, and low back pain. She had been taking phenazopyridine (*Pyridium*) 100 mg four times daily for approximately 2 years and had taken one dose of trimethoprim-sulfamethoxazole (*Bactrim DS*) the evening before the ED visit for a presumed urinary tract infection. Her other medications included lamotrigine, amitriptyline, venlafaxine XR, olanzapine, aspirin, diltiazem, simvastatin, hydrochlorothiazide, zolpidem, fentanyl patch, hydrocodone/acetaminophen as needed, and acetaminophen/codeine as needed. The patient's abdominal complaints were mostly suprapubic, and she had no complaints of shortness of breath, chest pain, or cyanosis.

Her vital signs included an oxygen saturation of 91% on room air, blood pressure 167/99, and respiratory rate of 18 breaths/min. She was afebrile. She received 3 L of oxygen by nasal cannula, and it only increased her oxygen saturation to 92%. CT of her abdomen and chest were normal. A notable laboratory abnormality was hemoglobin of 9.3 g/dL (reference range, female 12-15.5 g/dL). An arterial blood

gas (ABG) on 3 L of oxygen revealed pH 7.36 (reference range, 7.34-7.44), carbon dioxide 41 mm Hg (reference range, 33-45 mm Hg), oxygen 114 mm Hg (reference range, 75-105 mm Hg), serum bicarbonate 22.2 mEq/L (reference range, 22-26 mEq/L), oxygen saturation 97% (reference range, 96%-100%), and oxygen content 10.6 mL/dL (reference range, 15-33 mL/dL). Co-oximetry revealed a methemoglobin level of 11.4% (reference, <3%), carboxyhemoglobin 3.7% (reference, <2%), oxyhemoglobin 82.5% (reference range, 97%-100%). The patient had serial troponin levels of <0.04 ng/mL (reference, <0.04 ng/mL) at 14:56, 0.20 ng/mL at 18:41, 0.41 ng/mL at 01:20, and 0.33 ng/mL at 04:15. Methylene blue was not administered to the patient because she was asymptomatic and there were no new ischemic changes on her ECG. On discharge 2 days later, she had no evidence of cardiac ischemia and phenazopyridine and trimethoprim-sulfamethoxazole were not continued.

An acquired methemoglobinemia occurs when the oxygen carrying ferrous iron (Fe^{2+}) in the hemoglobin molecule is oxidized to the ferric state (Fe^{3+}) as a result of exposure to oxidizing drugs or their metabolites. Methemoglobin causes tissue hypoxia by 2 mechanisms: increased affinity for oxygen,

which shifts the oxygen dissociation curve to the left, and decreasing the amount of free hemoglobin available to transport oxygen. Phenazopyridine has long been known to cause methemoglobinemia as a result of its major metabolite, aniline.

Methemoglobinemia has been caused by phenazopyridine with normal dosing, overdose, and patients with decreased renal function. Trimethoprim-sulfamethoxazole has also been shown to cause methemoglobinemia. However an elevated troponin I secondary to methemoglobinemia has not previously been observed. This patient had a troponin leak that peaked at 10 hours.

The authors surmise that the patient had a pre-existing anemia (hemoglobin 9.3 g/dL) and a low oxygen saturation, which prompted them to look further into her condition. They point out that the patient was suffering from methemoglobinemia secondary to her phenazopyridine that was exacerbated by her recent addition of trimethoprim-sulfamethoxazole, and her pre-existing anemia caused sufficient hypoxia to cause stress ischemia (troponin leak) even in the absence of coronary artery disease.

Cannon RD, Wagner M, Jacoby JL. Troponin leak associated with drug-induced methemoglobinemia. *Am J Emer Med*. 2014;32:1295.e3-1295.e4. ■